Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

*PD MED Collaborative Group**

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*Members listed at end of paper

Correspondence to:
PD MED Trial Office, Birmingham Clinical Trials Unit, College of Medical and Dental Sciences, Robert Aitken Institute for Clinical Research, University of Birmingham, Birmingham B15 2TT, UK
PD-trials@bham.ac.uk

Summary

Background Whether initial treatment for Parkinson's disease should consist of levodopa, dopamine agonists, or monoamine oxidase type B inhibitors (MAOBI) is uncertain. We aimed to establish which of these three classes of drug, as initial treatment, provides the most effective long-term control of symptoms and best quality of life for people with early Parkinson's disease.

Methods In this pragmatic, open-label randomised trial, patients newly diagnosed with Parkinson's disease were randomly assigned (by telephone call to a central office; 1:1:1) between levodopa-sparing therapy (dopamine agonists or MAOBI) and levodopa alone. Patients and investigators were not masked to group assignment. Primary outcomes were the mobility dimension on the 39-item patient-rated Parkinson's disease questionnaire (PDQ-39) quality-of-life scale (range 0–100 with six points defined as the minimally important difference) and cost-effectiveness. Analysis was intention to treat. This trial is registered, number ISRCTN69812316.

Findings Between Nov 9, 2000, and Dec 22, 2009, 1620 patients were assigned to study groups (528 to levodopa, 632 to dopamine agonist, 460 to MAOBI). With 3-year median follow-up, PDQ-39 mobility scores averaged 1·8 points (95% CI 0·5–3·0, p=0·005) better in patients randomly assigned to levodopa than those assigned to levodopa-sparing therapy, with no increase or attrition of benefit during 7 years' observation. PDQ-39 mobility scores were 1·4 points (95% CI 0·0–2·9, p=0·05) better in patients allocated MAOBI than in those allocated dopamine agonists. EQ-5D utility scores averaged 0·03 (95% CI 0·01–0·05; p=0·0002) better with levodopa than with levodopa-sparing therapy; rates of dementia (hazard ratio [HR] 0·81, 95% CI 0·61–1·08, p=0·14), admissions to institutions (0·86, 0·63–1·18; p=0·4), and death (0·85, 0·69–1·06, p=0·17) were not significantly different, but the upper CIs precluded any substantial increase with levodopa compared with levodopa-sparing therapy. 179 (28%) of 632 patients allocated dopamine agonists and 104 (23%) of 460 patients allocated MAOBI discontinued allocated treatment because of side-effects compared with 11 (2%) of 528 patients allocated levodopa (p<0·0001).

Interpretation Very small but persistent benefits are shown for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy. MAOBI as initial levodopa-sparing therapy was at least as effective as dopamine agonists.

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Introduction

Parkinson's disease is a common cause of disability in older people with 8000 new cases diagnosed every year in the UK, and more than 100 000 people living with the disease.[1,2] Of the three classes of drug widely used as initial therapy, levodopa achieves somewhat better control of motor symptoms of Parkinson's disease than do dopamine agonists and monoamine oxidase type B inhibitors (MAOBI), but abnormal involuntary movements (dyskinesias) and fluctuations in motor control develop after long-term use or high-dose treatment.[3,4] Motor complications are seen less frequently with dopamine agonists and MAOBI than with levodopa, suggesting that longer-term symptomatic control could be better with levodopa-sparing therapy than with levodopa. However, non-motor side-effects such as nausea, hallucinations, oedema, and sleep disturbance are more frequent with dopamine agonists than with levodopa,[5,6] and could be more important for patients and carers than are motor complications.[5] Safety is another issue, with higher mortality reported with the MAOBI, selegiline, than with levodopa alone in the UKPDRG study,[7] although this has not been confirmed in other studies.[6] Conversely, the DATATOP study[8] raised the possibility that selegiline slows functional decline.

Because most previous studies included too few patients, had short follow-up, and assessed motor symptoms rather than the effect of the drugs on the patient's self-rated overall quality of life, uncertainty remains regarding the comparative balance of risks and

benefits of initiation of treatment with these different classes of drugs for Parkinson's disease.[9] Costs vary substantially; the new dopamine agonists and MAOBIs cost more than do either levodopa or selegiline, and large, long-term randomised studies are needed to compare the clinical and cost-effectiveness of the different drug classes, detect any neuroprotective effects,[10] and clarify how they should best be used in clinical practice.[11]

We aimed to establish which class of drug results in the best patient-rated quality-of-life scores, in both early and later Parkinson's disease. We describe the first results of the early disease randomisation, which addressed two questions: (1) does initial treatment with levodopa-sparing therapy (either a dopamine agonist or an MAOBI) delay deterioration in patient-rated quality of life compared with levodopa alone; and (2) which class of levodopa-sparing treatment is preferable (dopamine agonists or MAOBI)?

Methods

Study design and participants

For this pragmatic, open-label randomised trial (PD MED), people diagnosed with idiopathic Parkinson's disease by movement disorder specialists using UK Brain Bank Diagnostic Criteria[12] were eligible if they were previously untreated, or had been treated for less than 6 months with dopaminergic drugs and if there was uncertainty as to which class of drug to use. Exclusion criteria included dementia and inability to complete trial questionnaires. Ethics approval was provided by the West Midlands Research Ethics Committee, local approval was obtained at each participating centre, and all patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive either levodopa, dopamine agonists, or MAOBI by telephone call to the central randomisation service at the University of Birmingham (Birmingham, UK). Either MAOBI or levodopa could be omitted from the randomisation if considered inappropriate for a particular patient. Randomisation was minimised by previous levodopa therapy (none, <1, 1–2, 3–5 months), Hoehn and Yahr disease stage, and age (<50, 50–59, 60–69, 70–79, ≥80 years). Patients and investigators were not masked to group assignment.

Procedures

The pragmatic trial design aimed to facilitate large-scale recruitment of a heterogeneous group of patients, allowing investigators to start open-label treatment with whichever drug they preferred within the allocated class and to titrate the dose of levodopa and dopamine agonists within the bounds of the product licence. If symptoms were not controlled by the standard dose of MAOBI or the maximum tolerated dose of dopamine agonist, investigators could add levodopa as needed. Otherwise, adding or switching to a new drug from another drug class was only permissible if patients' symptoms were still not adequately controlled, or for adverse effects.

For the **study protocol** see http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/pd/pdmed/investigators/documentation.aspx

Outcomes

One primary outcome was patient-rated functional status on the mobility subscale of the 39-item Parkinson's Disease Questionnaire (PDQ-39).[13] The PDQ-39 assesses the effect of Parkinson's disease on quality of life, and is sensitive to changes regarded as important to patients, but not identified by clinical rating scales. The second primary outcome was quality-adjusted life-years (QALYs) derived from the EuroQol EQ-5D[14] generic quality-of-life measure and a resource usage questionnaire. Cost utility analyses will be reported separately. Secondary outcome measures included the other PDQ-39 domains and overall score (summary index), compliance, cognition

For more on **EuroQol EQ-5D** see www.euroqol.org

	Randomisation option			Levodopa *vs* levodopa sparing comparison		Levodopa-sparing comparison (dopamine agonist *vs* MAOBI)	
	3-way (levodopa *vs* dopamine agonist *vs* MAOBI; n=1058)	2-way (levodopa *vs* dopamine agonist; n=348)	2-way (dopamine agonist *vs* MAOBI; n=214)	Levodopa (n=528)	Levodopa-sparing (n=878)	Dopamine agonist (n=459)	MAOBI (N=460)
Age (years)	71 (34–94)	71 (44–93)	62 (27–85)	71 (34–94)	71 (42–92)	69 (27–92)	69 (36–92)
Men	686 (65%)	225 (65%)	141 (66%)	338 (64%)	573 (65%)	284 (62%)	315 (68%)
Patients with regular carer	664 (63%)	198 (57%)	114 (53%)	324 (61%)	538 (61%)	289 (63%)	269 (58%)
Duration of Parkinson's disease (years)	0·6 (0–13)	0·6 (0–6)	0·7 (0–5·5)	0·6 (0–10)	0·6 (0–13)	0·6 (0–6)	0·7 (0–13)
Hoehn and Yahr stage 1–1·5	479 (45%)	189 (54%)	147 (69%)	254 (48%)	414 (47%)	232 (51%)	235 (51%)
Hoehn and Yahr stage 2	320 (30%)	97 (28%)	47 (22%)	155 (29%)	262 (30%)	130 (28%)	130 (28%)
Hoehn and Yahr stage 2·5–5	259 (25%)	62 (18%)	20 (9%)	119 (23%)	202 (23%)	97 (21%)	95 (21%)
Previously received anti-Parkinsonian treatments	88 (8%)	32 (9%)	16 (7%)	46 (9%)	74 (8%)	37 (8%)	38 (8%)
PDQ-39 mobility score	30·3 (25·8)	32·2 (26·4)	21·2 (22·3)	31·2 (25·5)	30·5 (26·2)	28·3 (26·5)	27·7 (24·6)
PDQ-39 summary index	22·3 (13·7)	22·8 (13·9)	19·8 (11·9)	22·6 (13·2)	22·3 (14·0)	21·7 (13·5)	21·4 (13·2)

Data are mean (range), n (%), or mean (SD). PDQ=Parkinson's disease questionnaire. MAOBI=monoamine oxidase type B inhibitor.

Table 1: **Demographic and baseline characteristics by randomisation option and by protocol comparison**

using mini-mental state examination (MMSE), onset of dementia, dyskinesias and motor fluctuations, admissions to hospital or institutional care, and mortality. Patients completed study forms before randomisation and, by post, at 6 months, 1 year, and thereafter annually. The MMSE was administered at baseline, 5 years, and 10 years. Information about disease status (Hoehn and Yahr stage, any change in Parkinson's disease diagnosis), motor complications, treatment compliance, side-effects, dementia diagnoses, and admissions to institutions was collected systematically at annual clinical assessments and on serious adverse event forms. Mortality was monitored through the National Health Service Information Centre.

Statistical analysis

We designed PD MED to detect a six-point minimum clinically meaningful difference between groups in the PDQ-39 mobility domain at any one timepoint. We assumed a SD of 18·6, which required 300 patients in each arm for 90% power at $p<0·01$. To allow for a 10% withdrawal rate and for the two-way randomisation options, target recruitment was 1500 patients. The study closed to recruitment, with 1620 randomised, when the parallel randomisation in later disease reached its 500-patient recruitment target.

Analyses were by intention to treat, including all available data irrespective of treatment compliance, and stratified by randomisation option. Continuous outcome measures were analysed with mixed effect repeated measures models with baseline scores included as a covariate. Missing items in PDQ-39 domain scores were imputed with an expectation maximisation algorithm.[15,16] Missing assessments were not imputed. Time-to-event data were compared with log-rank methods. MMSE scores were compared with *t* tests. Side-effects and serious adverse events were compared with Fisher's exact test. Comparisons of overall drug doses use levodopa equivalent doses (LED).[17] p values do not allow for multiple significance testing. Variability in treatment effect across protocol-specified stratification parameters was explored with tests of heterogeneity or trend.

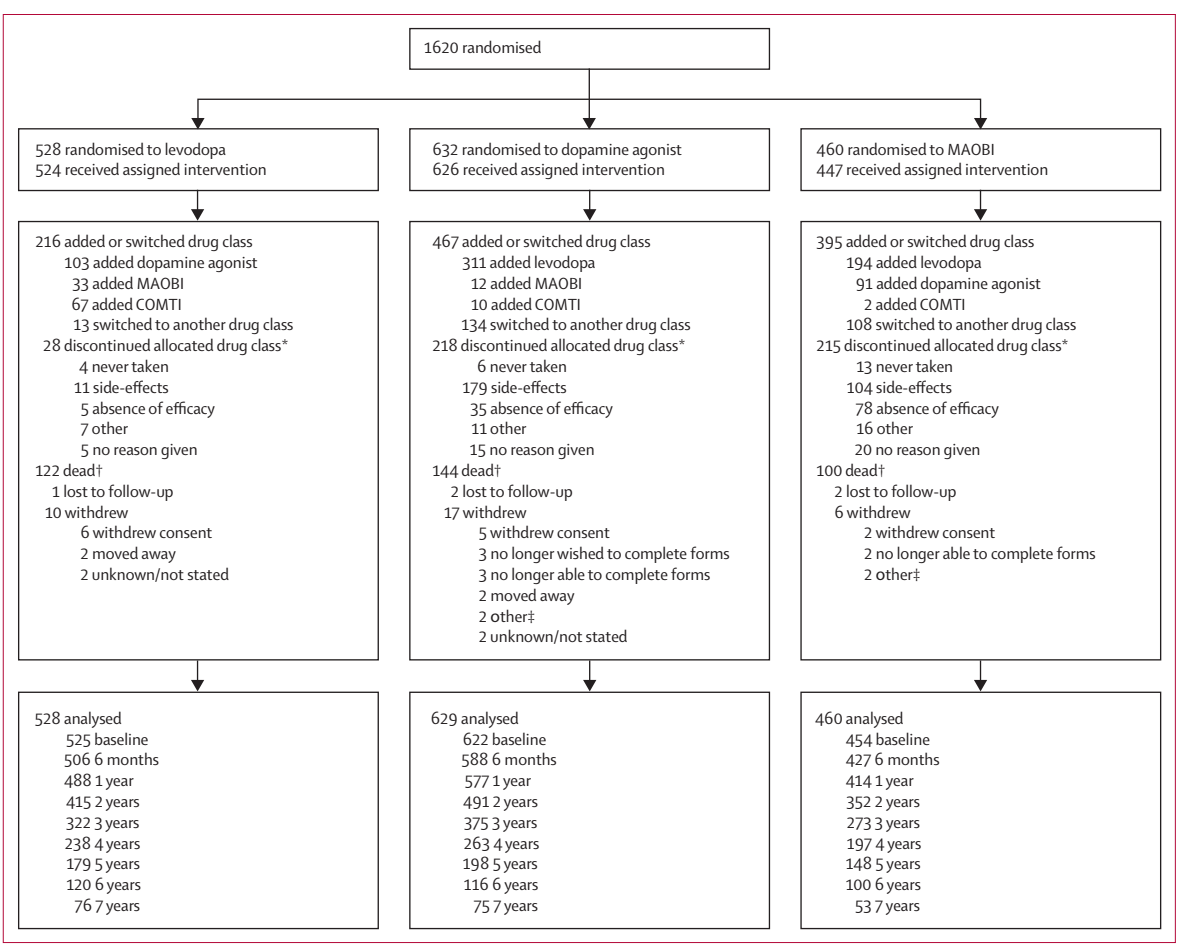

Figure 1: **Trial profile**

MAOBI=monoamine oxidase type B inhibitors. COMTI=catechol-O-methyl transferase inhibitors. *Reasons for discontinuing drug class are not mutually exclusive, some patients had more than one reason for stopping drug class usually side-effects and absence of efficacy. †14 patients withdrew or were lost to follow-up then later died (five for levodopa group, eight for dopamine agonist, one for MAOBI). ‡Other reason normally comorbidity.

We used SAS version 9.2 for analyses. Interim analyses of unmasked efficacy and safety data were reviewed annually by an independent data monitoring committee.

The trial is registered, number ISRCTN69812316.

Role of the funding source

The funders had no role in study design, conduct, or reporting. The writing committee had full access to all data, and were responsible for the decision to publish.

Results

Between Nov 09, 2000, and Dec 22, 2009, 1620 people with early Parkinson's disease were assigned to treatment groups in PD MED from 89 UK neurology and geriatric clinics, one Czech, and one Russian site. 1058 (65%) of 1620 were randomly assigned three ways between dopamine agonists, MAOBI, and levodopa, 348 (21%) were assigned two ways between dopamine agonists and levodopa, and 214 (13%) were assigned two ways between dopamine agonists and MAOBI (table 1; figure 1). Thus, in total, 1406 were randomised between levodopa-sparing therapy and levodopa, and 919 between the two levodopa-sparing therapies, dopamine agonists and MAOBI. Patients assigned only between dopamine agonists and MAOBI had less severe disease and were younger, with a mean age of 62 years compared with 71 years in the other two randomisation options. Other patient characteristics were balanced between randomisation and treatment groups. 136 (8%) of 1620 patients had previously received dopaminergic treatment. If allocated dopamine agonists, clinicians for 887 (55%) of 1620 patients intended to use ropinirole, 468 (29%) of 1620 to use pramipexole, and less than 5% each one of six other agonists (bromocriptine [71/1620], cabergoline [65/1620], pergolide [53/1620], piribedil [24/1620], rotigotine [17/1620], and lisuride [1/1620]. The intended MAOBI was oral selegiline for 842 (66%) of 1272 patients, sublingual selegiline for 142 (11%) of 1272, and rasagiline for 266 (21%) of 1272 patients.

Median follow-up was 3 years (range 0–9). The diagnosis of idiopathic Parkinson's disease was revised for 79 (5%) of 1620 patients, most to Parkinson's disease-plus syndrome. 1601 (99%) of 1620 patients had complete PDQ-39 data at baseline, 1521 (95%) of 1601 at 6 months, 1479 (94%) of 1581 at 1 year, 1258 (91%) of 1379 at 2 years, 970 (88%) of 1101 at 3 years, 698 (85%) of 821 at 4 years, 525 (83%) of 636 at 5 years, 330 (76%) of 443 at 6 years, and 204 (75%) of 271 at 7 years. We noted no significant differences between randomisation arms in numbers with missing assessments (figure 1, appendix). Few patients had assessments beyond 7 years and, accordingly, analyses of continuous outcome measures (eg, PDQ-39) include data up to 7 years only.

For compliance, participants allocated MAOBI or dopamine agonists were significantly more likely to discontinue their allocated drug class than those allocated levodopa: 7-year probabilities were 72% for MAOBI, 50% for dopamine agonists, and 7% for levodopa ($p<0·0001$, figure 2). This difference was mainly attributable to side-effects with 179 (28%) of 632 allocated dopamine agonists and 104 (23%) of 460 allocated MAOBI discontinuing because of side-effects compared with 11 (2%) of 528 allocated levodopa ($p<0·0001$, appendix). The side-effects (mainly psychological, sleep disturbance, and gastrointestinal) were usually mild, only 16 patients (nine given dopamine agonists, four given MAOBI, and three given levodopa) had serious adverse events believed to be possibly related to trial treatment. 35 (6%) of 362 allocated dopamine agonists and 78 (17%) of 460 allocated MAOBI were stopped because of an absence of efficacy compared with five (1%) of 528 in the levodopa group ($p<0·0001$). Of those patients who stopped dopamine agonists, 169 (78%) of 218 switched to levodopa, ten (5%) of 218 switched to MAOBI, and 17 (8%) of 218 to catechol O-methyltransferase inhibitors (COMTI). Of those stopping MAOBI, 102 (48%) of 215 changed to levodopa, 88 (41%) of 215 to dopamine agonists, and nine (4%) of 215 to COMTI. In the levodopa group, 11 (39%) of 28 switched to dopamine agonists.

Participants allocated and still taking MAOBI or dopamine agonists were also significantly more likely than those allocated levodopa to need a drug from another class added to their treatment: 2-year probabilities were 64% for MAOBI, 40% for dopamine agonists, and 20% for levodopa ($p<0·0001$, appendix). Of 333 patients in the dopamine agonist group, 311 (93%) added levodopa alone, 12 (4%) added MAOBI, and ten (3%) added COMTI. However, of 287 in the MAOBI group, 194 (67%) added levodopa, 91 (32%) added dopamine agonists, and two (1%) added COMTI. Finally, of 203 patients in the levodopa group, 103 (51%)

See Online for appendix

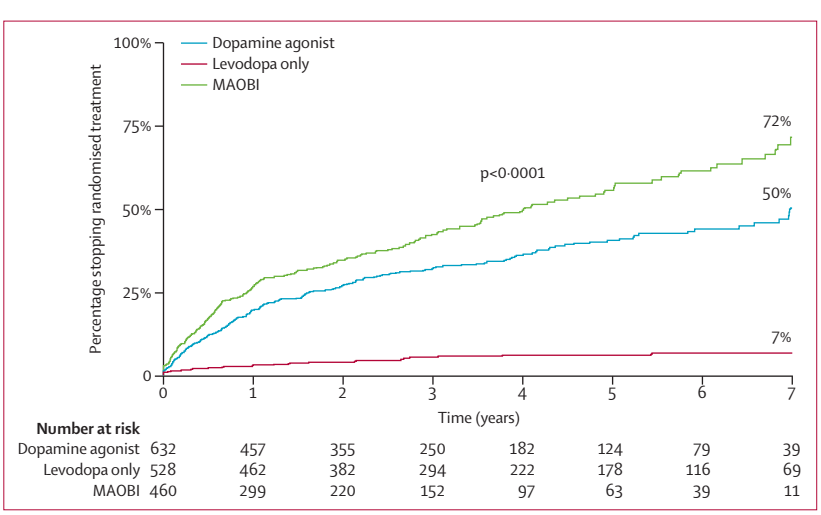

Figure 2: **Proportion of patients stopping treatment with allocated drug class**
MAOBI=monoamine oxidase type B inhibitors.

added dopamine agonists, 33 (16%) added MAOBI, and 67 (33%) added COMTI.

Exposure to levodopa was, however, similar in the dopamine agonists and MAOBI groups: averaging in all patients at 1 year, 96 mg/day (SD 157) for dopamine agonists and 131 mg/day (172) for MAOBI, rising at 7 years to 526 mg/day (266) for dopamine agonists and 489 mg/day (246) for MAOBI. The mean daily dose in patients allocated levodopa was 347 mg (SD 139) at 1 year rising to 531 mg (229) at 7 years (appendix). For patients allocated dopamine agonists and taking ropinirole, mean dose was 9 mg/day (SD 4·5) at 1 year rising to 13 mg/day (6·7) at 7 years. For pramipexole, mean dose was 2·2 mg/day (1·1; salt) at 1 year rising to 3·4 mg/day (SD 1·5) at 7 years. The mean doses for MAOBI remained constant: 8·4 mg/day (SD 3·1) for selegiline and 1·0 mg/day (0·1) for rasagiline at 1 year compared with 8·6 mg/day (2·7) for selegiline and 1·0 mg/day (0·0) for rasagiline at 7 years. Converting drug doses into LED,[18] showed that LED was similar at 1 year in the dopamine agonists (269 mg/day [SD 155]) and MAOBI groups (247 mg/day [154]), but significantly (p<0·0001) higher in the levodopa group (354 mg/day [136]). By 7 years, LED had risen to 636 mg/day (SD 298) in the levodopa group, 695 mg/day (329) in the MAOBI group, and 768 mg/day (387) in the dopamine agonist group (figure 3).

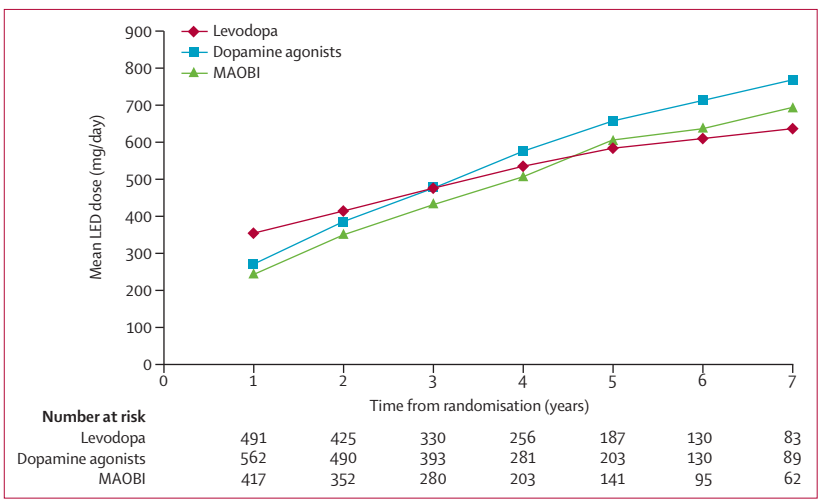

Figure 3: **Mean levodopa equivalent dose (LED; mg per day) by allocated treatment**
MAOBI=monoamine oxidase type B inhibitors.

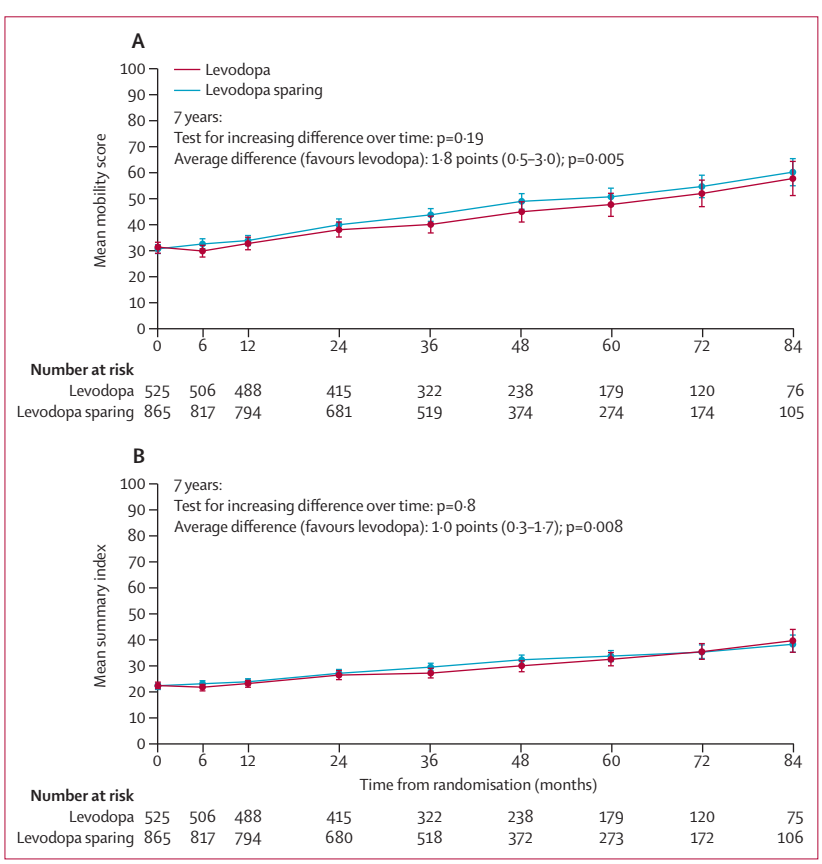

Figure 4: **39-item patient-rated Parkinson's disease questionnaire mobility score (A) and summary index (B) with time in levodopa and levodopa-sparing groups**

PDQ-39 mobility scores did not differ significantly between the levodopa group and levodopa-sparing group at any follow-up assessment (figure 4A). However, the average score during the first 7 years of follow-up was 1·8 points (95% CI 0·5–3·0, p=0·005) better with levodopa than with levodopa-sparing therapy, with no significant divergence or convergence in this efficacy estimate (p=0·19). Scores on the activities of daily living (ADL), stigma, cognition, communication, and bodily discomfort subscales were also significantly (p<0·05 without allowance for multiple significance testing) better with levodopa than with levodopa-sparing therapy (table 2). The levodopa group averaged 1·0 points higher in PDQ-39 summary index than did the levodopa-sparing group (95% CI 0·3–1·7, p=0·008) with no significant increase or attrition of benefit during follow-up (figure 4B). Scores for the EuroQol EQ-5D utility measure averaged 0·03 (95% CI 0·01–0·05, p=0·0002) better with levodopa than with levodopa-sparing therapy (table 2, appendix). The clinically rated Hoehn & Yahr disease stage scores were also on average 0·07 (95% CI 0·03–0·12, p=0·0009) points better with levodopa than with levodopa-sparing therapy (appendix).

Patients in the levodopa group were more likely to develop dyskinesias than those in the levodopa-sparing group (hazard ratio [HR] 1·52, 95% CI 1·16–2·00, p=0·003; figure 5), but there was no difference in motor fluctuations (1·11, 0·90–1·37, p=0·3; appendix). 5-year decline in MMSE was similar (1·9 [SD 4·1] with levodopa and 1·9 [4·4] with levodopa-sparing therapy p=0·9), and although fewer patients in the levodopa than in the levodopa-sparing group developed dementia (HR 0·81, 95% CI 0·61–1·08, p=0·14, appendix); fewer entered institutional care (0·86, 0·63–1·18; p=0·4, appendix); and fewer died (0·85, 0·69–1·06, p=0·17, appendix), none of these differences were statistically significant.

Treatment efficacy, as measured by PDQ-39 mobility subscale, did not differ according to baseline stratification variables (age, Hoehn and Yahr stage, and duration of Parkinson's disease symptoms). In particular, the advantage of levodopa compared with levodopa-sparing therapy was similar in patients younger than and older than age 70 years (appendix).

PDQ-39 mobility scores averaged 1·4 points (95% CI 0·0–2·9, p=0·05) better in patients initiating therapy with MAOBI than those initiating dopamine agonists (figure 6A). Significantly better scores on the cognition subscales were also seen with MAOBI compared with dopamine agonists (table 2), and PDQ-39 summary index averaged 0·8 points (95% CI 0·0–1·7, p=0·05) better in participants allocated MAOBI as initial therapy than in those allocated dopamine agonists (figure 6B). There was no difference in scores on the EuroQol EQ-5D generic quality-of-life measure: 0·004 (95% CI −0·01 to 0·02; p=0·6; table 2, appendix). Hoehn and Yahr disease stage scores averaged 0·05 (95% CI 0·00–0·10, p=0·05) points better with MAOBI than with dopamine agonists (appendix).

Rates of dyskinesia were similar (HR 0·85, 95% CI 0·60–1·22, p=0·4), but motor fluctuations were higher (HR 1·32, 95% CI 1·01–1·72, p=0·04) in the dopamine agonist group than in the MAOBI group (appendix). 5-year decline in MMSE was greater in participants allocated dopamine agonists than in those allocated MAOBI (2·4 [SD 4·4] *vs* 1·3 [3·7], p=0·04), but there was no significant difference in the number of patients developing dementia (HR 1·11, 95% CI 0·77–1·59, p=0·6; appendix), entering institutional care (1·08, 0·70–1·64, p=0·7, appendix), or dying (0·96, 0·73–1·28, p=0·8, appendix).

	Levodopa *vs* levodopa-sparing		Dopamine agonist *vs* MAOBI		MID*
	Estimate† (95% CI)	p value	Estimate‡ (95% CI)	p value	
Mobility	1·8 (0·5 to 3·0)	0·005	1·4 (0·0 to 2·9)	0·05	3·2
ADL	1·9 (0·7 to 3·0)	0·002	0·3 (−1·1 to 1·7)	0·7	4·4
Emotional wellbeing	−0·2 (−1·1 to 0·7)	0·7	0·3 (−0·8 to 1·4)	0·6	4·2
Stigma	1·3 (0·2 to 2·3)	0·02	1·3 (0·0 to 2·5)	0·06	5·6
Social support	0·1 (−0·6 to 0·8)	0·8	0·8 (−0·1 to 1·7)	0·07	11·4
Cognition	1·0 (0·0 to 2·0)	0·05	1·7 (0·5 to 2·9)	0·005	1·8
Communication	0·9 (0·0 to 1·8)	0·05	0·5 (−0·6 to 1·5)	0·4	4·2
Bodily discomfort	1·4 (0·3 to 2·4)	0·01	0·7 (−0·6 to 2·0)	0·3	2·1
Summary index	1·0 (0·3 to 1·7)	0·008	0·8 (0·0 to 1·7)	0·05	1·6
EQ-5D utility score	0·03 (0·01 to 0·05)	0·0002	0·004 (−0·01 to 0·02)	0·6	..

PDQ=Parkinson's disease questionnaire. MAOBI=monoamine oxidase type B inhibitor. ADL=activities of daily living. *MID=minimally important difference.[12] †Positive numbers favour levodopa. ‡Positive numbers favour MAOBI.

Table 2: **Estimated average differences between levodopa and levodopa-sparing groups, and between dopamine agonist and MAOBI, in the different PDQ-39 subscales and in EQ-5D utility score**

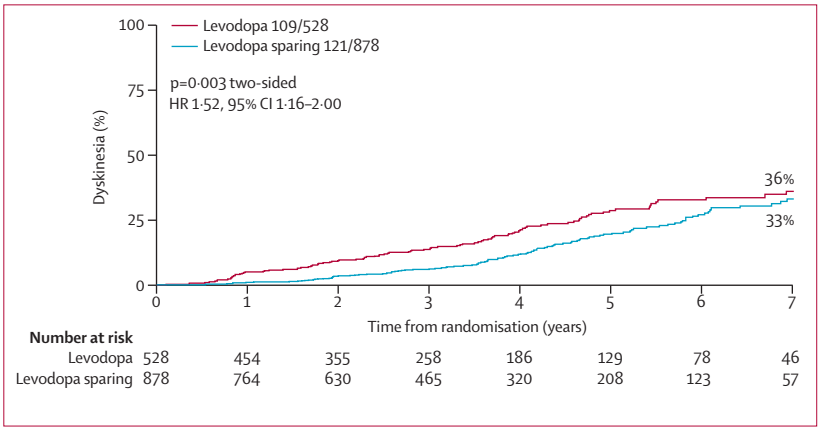

Figure 5: **Risk of developing dyskinesia in levodopa and levodopa-sparing groups**

Discussion

Generally, levodopa is accepted to provide better short-term control of the motor symptoms of newly diagnosed Parkinson's disease and fewer side-effects than do dopamine agonists or MAOBIs, but motor complications are increased (panel). We show that the overall balance of benefits and risks favours levodopa over levodopa-sparing therapy with better patient-rated quality of life both in the short and long term. Levodopa treatment achieved better scores than did dopamine agonists or MAOBIs on the primary PDQ-39 mobility outcome, and a range of other patient-rated outcome measures, including ADL and overall quality of life as measured by the PDQ-39 disease-specific and EQ-5D generic quality-of-life measures. Clinician-rated disease status by Hoehn and Yahr staging was also significantly improved. These benefits were seen despite levodopa-treated patients developing more involuntary movements though, notably, no more motor fluctuations.

The 1·8 PDQ-39 mobility and 1·0 summary index points favouring initial levodopa compared with levodopa-sparing therapy are, however, below the predefined six-point threshold thought, when PD MED was designed, to be the minimum clinically important difference (MCID), and below a subsequent, smaller MCID estimate of 3·2 points.[17] The corresponding standardised effect sizes[24] are 0·09 SD and 0·07 SD, below the 0·2 SD threshold categorised as a small treatment effect.[25] Expressed in relation to rate of decline,[26] these treatment benefits correspond to around 5 months and 4 months progress of the disease, respectively—less than the 6-month disease progress MCID threshold cited in dementia studies using annual decline methods.[26,27] Thus, the benefits of levodopa compared with levodopa-sparing are unquestionably small.

A clinically relevant finding, though, is that during 7 years of follow-up, we showed no indication of any cumulative adverse effect of levodopa therapy, with no loss of benefit with time. The lower rates of admissions to institutions, dementia, and death were not statistically significant, but the upper CIs preclude any substantial increase with levodopa compared with levodopa-sparing therapy. Thus, there seem to be no grounds for concerns that use of levodopa as first-line therapy results in worse long-term outcome. The better quality-of-life scores with

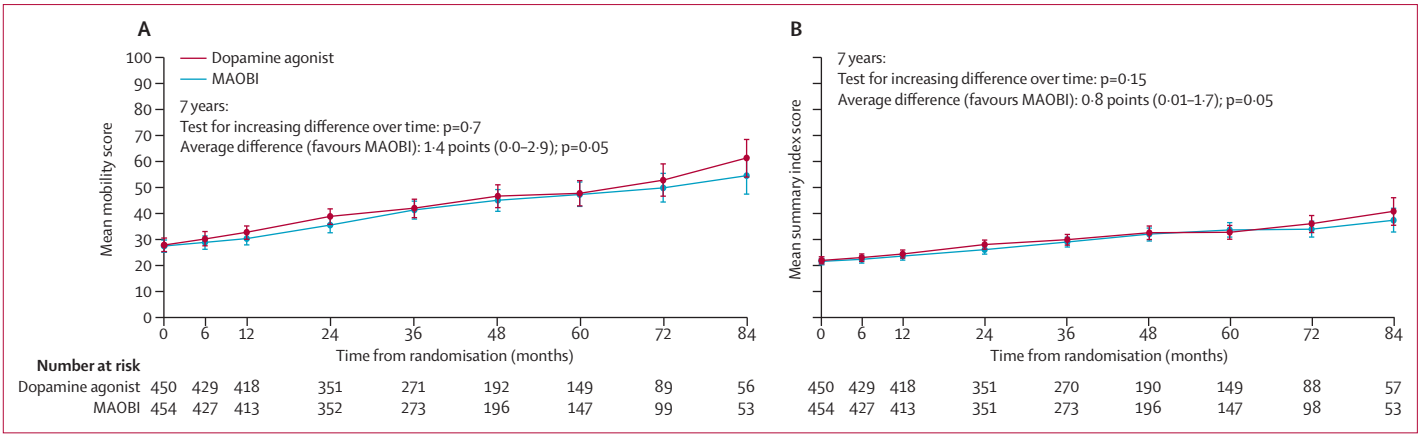

Figure 6: **39-item patient-rated Parkinson's disease questionnaire mobility score (A) and summary index (B) with time in dopamine agonist and MAOBI groups**
MAOBI=monoamine oxidase type B inhibitors.

Panel: Research in context

Systematic review

We updated our previously described searches of Medline, Embase, and the Cochrane Central Register of Controlled Trials on June 5, 2014, and identified only one additional randomised trial (n=91) of a dopamine agonist, cabergoline, versus levodopa[19] in addition to the 5247 patients in 29 trials of dopamine agonists and 3525 patients in 17 trials of MAOBI therapy in early Parkinson's disease that we previously described.[5,6,20–23] Motor complications were reduced with dopamine agonists compared with levodopa, but other important side-effects were increased and short-term symptom control was poorer.[5] Monoamine oxidase type B inhibitors (MAOBIs) also reduced clinician-rated disability, the need for levodopa, and the incidence of motor fluctuations compared with levodopa, without substantial side-effects or increased mortality.[6] Both reviews[5,6] concluded that the balance of benefits and risks remains uncertain, and that further large, long-term comparative trials were necessary, including patient-rated quality-of-life measures.

Interpretation

The PD MED trial, with 7 years of follow-up, shows small but persistent benefits in patient-rated mobility scores and overall quality of life from initiating therapy with levodopa compared with levodopa-sparing therapy. MAOBI appeared at least as effective as dopamine agonists as levodopa-sparing therapy.

levodopa at earlier assessments might be partly explained by higher LED dose treatment in the levodopa group than in the dopamine agonists and MAOBI groups. However, by 7 years, the dopamine agonists group was receiving higher LED treatment than were the levodopa and MAOBI groups, yet there was no suggestion that the advantage of initial treatment with levodopa and MAOBI over dopamine agonists diminished over 7 years of follow-up.

In cases for which levodopa-sparing therapy is deemed appropriate, dopamine agonists are generally preferred to MAOBIs, which are perceived as less effective. However, we noted small—ie, below MCID thresholds—but significant benefits favouring initial treatment with MAOBI compared with dopamine agonists in PDQ-39 mobility, cognition, and summary index scores, but not in EQ-5D. Although more patients discontinued MAOBI than they did dopamine agonists, the benefits of MAOBI compared with dopamine agonists are not explained by readier addition of other drugs because the LED was higher in the dopamine agonists group than in the MAOBI group throughout the first 7 years of treatment. A possible explanation for the lesser efficacy of dopamine agonists, despite the higher LED, is that levodopa could be less effective when added to dopamine agonists than MAOBI, because dopamine agonists and levodopa both act on D2 class receptors—with levodopa also stimulating dopamine D1 receptors—so the efficacy of the combination might be less than additive. Notably, the onset of dyskinesia was not significantly higher with MAOBI than with dopamine agonists, and fewer motor fluctuations were reported with initial MAOBI therapy, so avoiding motor complications should not be a reason to prefer dopamine agonists over MAOBI therapy.

A full cost-utility analysis will be reported separately. However, because other outcome measures—including major cost-drivers such as admissions to institutions and development of dementia—consistently favour levodopa over levodopa-sparing therapy the economic analyses are also likely to favour the substantially less expensive levodopa therapy. Similarly, because MAOBIs, particularly selegiline, cost less than do dopamine agonists and achieved at least as good results, they are likely to be shown in cost-utility analyses to be more cost effective.

In present clinical practice, patients younger than 60 years are treated initially with either a dopamine agonist or MAOBI to avoid levodopa-related motor complications. Levodopa tends to be used in patients older than 70 years for whom long-term complications are judged less important. Subgroup comparisons in PD MED noted no difference in treatment efficacy in those younger than and older than 70 years and hence do not support age-specific treatment recommendations. However, as seen in studies of Parkinson's disease incidence,[1,28] few participants (12%) were younger than 60 years at randomisation, particularly in the levodopa versus levodopa-sparing comparison, so

the trial provides little direct evidence for how such patients should be treated.

The significant benefits of initial therapy with MAOBI compared with dopamine agonists in PDQ-39 cognition score and decline in MMSE, but not in development of dementia, could reflect a disease-modifying effect—long hypothesised for MAOBI treatment[8]—but might also be explained by an alerting effect of the amphetamine metabolites of selegiline, or an antidepressant effect of MAOBIs, or chance. Longer-term follow-up of PD MED will be informative.

Missing data can be a source of bias in studies with symptom ratings as outcome, particularly if levels of missing outcome data differ between treatment groups. Although reasons for stopping treatment differed across the drugs in PD MED, patients who stopped their randomised treatment still continued to complete patient questionnaires, and outcome data were available for most such patients. Also, the repeated measures analyses include all available data so patients who miss some assessments still contribute to estimates of treatment efficacy. Hence, given the low level of missing data, we do not consider that any bias from missing data could be of sufficient size to materially alter the study conclusions.

Another potential weakness of PD MED was open-label treatment, which could have introduced assessment bias. However, any such bias is probably small because all patients received active treatment, and would also be likely to favour levodopa-sparing therapy, particularly dopamine agonists, because the results are opposite to the a-priori expectations of most clinicians and patients. Open-label treatment, and patient-rated outcome measures, reduce trial costs and complexity, and this helped PD MED to recruit more patients than any previous trial of Parkinson's disease treatment.

Patient-reported outcome measures have not been widely used previously—an omission in previous trials—but similar treatment differences were seen with clinician-rated disease status and patient-rated outcomes, as previously reported with PDQ-39 and the clinician-rated UPDRS in the PD SURG trial.[29] Also, with few eligibility restrictions, a fairly typical group of patients with Parkinson's disease who would be candidates for dopaminergic treatment in a clinical setting were included, diagnostic accuracy was high, and compliance similar to that in previous studies. The large sample enhances statistical reliability and the so-called real world trial design arguably provide results that are more generalisable to typical patients and, as a result, more valuable in clinical practice than are less pragmatic studies. Another potential limitation of the study was the long period between initiation and availability of the results. However, the findings remain highly relevant with, for example, National Institute for Health and Care Excellence awaiting the findings before updating their treatment guidelines.[30]

In conclusion, no short-term or long-term benefit was seen from initiation of treatment of patients with early Parkinson's disease with levodopa-sparing therapy—dopamine agonists or MAOBI—rather than levodopa. If levodopa-sparing therapy is preferred, starting with MAOBIs seems to be at least as effective as with dopamine agonists.

Contributors

RG, CEC, AG, CJ, KW, and AW designed the trial. RG, CEC, KW, AW, NI, SP, and CR ran the trial and CEC and AW recruited patients. NI and SP analysed the data. RG, CEC, AG, NI, CJ, EM, SP, CR, KW, and AW interpreted the data and wrote the paper. The authors assume responsibility for the accuracy and completeness of the data and for the overall content and integrity of the paper.

UK PD MED Collaborative Group

Writing committee: Richard Gray (University of Oxford, Oxford, UK), Natalie Ives (University of Birmingham, Birmingham, UK), Caroline Rick (University of Birmingham, Birmingham, UK), Smitaa Patel (University of Birmingham, Birmingham, UK), Alastair Gray (University of Oxford, Oxford, UK), Crispin Jenkinson (University of Oxford, Oxford, UK), Emma McIntosh (University of Glasgow, Glasgow, UK), Keith Wheatley (University of Birmingham, Birmingham, UK), Adrian Williams (Queen Elizabeth Hospital, Birmingham, UK), Carl E Clarke (University of Birmingham, Birmingham, UK; Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK).
Data monitoring committee: P Sandercock (chair), C Baigent, P Crome.
Steering committee: A Williams (chair), R Abbott, M Baker, B Castleton, C E Clarke, C Counsell, AK Deb, S Fairweather, R Fitzpatrick, A Gray, N Ives, C Jenkinson, G MacPhee, T Malone, D Mant, E McIntosh, A Ming, P Morrish, P Ohri, V Pearce, B Wood, P Worth.
Trial management: P Au, T Boodell, V Cheed, C E Clarke, J Daniels, F Dowling, A Edmondson, R Gray, R Hawker, C Herd, N Hilken, N Ives, S Kaur, R Ottridge, S Patel, L Peto, C Rick, C Sidile, C Tomlinson, E Tyler, K Wheatley, N Winkles (Birmingham Clinical Trials Unit University of Birmingham)
Health Economics: A Gray (University of Oxford), E McIntosh, S Kent (University of Glasgow).
Quality-of-life: R Fitzpatrick, C Jenkinson (University of Oxford)
Participating centres and PD MED collaborative group members (* indicates current principal investigator at that centre)
Aberdeen Royal Infirmary L Caie, R Caslake, R Coleman, C Counsell*, P Crowley, L Gerrie, J Gordon, C Harris, V Leslie, M A Macleod, K Taylor (number of patients 67); *Addenbrooke's Hospital, Cambridge* R Barker, D Forsyth, M Halls, G Lennox*, J Young (28); *Arrowe Park Hospital, Wirral* E Azie, J Barrett*, A Monaghan, C Turnbull, H Vanek (56); *Bedford Hospital, Bedford* D Blake, M Manford*, N Thangarajah (5); *Birmingham Heartlands Hospital, Birmingham* M Johnson, P Wallis* (7); *Bishop Auckland General Hospital* P Carr, L Cochrane, R Prescott*, A Rose (15); *Borders General Hospital, Melrose* M Drover, P Karunaratne, A McLaren* (28); *Bridlington & District Hospital, Bridlington* E Jones*, M Nasar (8); *Brighton General Hospital, Brighton* M Bayliss* (1); *Bronglais General Hospital, Aberystwyth* P Jones*, B Lewis (2); *Bronllys Hospital, Brecon* A Dunn*, M Eckley, J Price, G Woodman (12); *Brookfields Hospital, Cambridge* D Forsyth*, M Halls, J Young (4); *Bucknall Hospital, Stoke on Trent* G Aldridge, N Bhuvanendran, S Lewis, C Mann*, K Patel (3); *Calderdale Royal Hospital, Halifax* N Ghaus, A Grueger, B Mallinson, G Wihl* (11); *City Hospital, Birmingham* S Ballantyne, CE Clarke*, S Coyle, R Hornabrook, S Hutchinson, H Irfan, A Lewthwaite, D Nicholl, S Poxon, A Ritch (146); *City Hospitals, Sunderland* J Davison, S Dodds, C Gray, U Nath*, G Robinson (9); *Colchester General Hospital, Colchester* A Deb, N Aftab*, D Read, L Villanueva (7); *Darlington Memorial Hospital, Darlington* L Alderton, P Carr*, L Cochrane, R Prescott, A Rose (10); *Delancey Hospital, Cheltenham* E Burrows, P Fletcher*, E Folkes, A Gilbert, H Hayes, P Morrow, M Silva (36); *Dumfries & Galloway Royal Infirmary, Dumfries* G Baxter, J Bell, J Gorman, J Lawrence, G Rhind* (5); *Eryri Hospital, Caernarfon* J Hindle, J Jones, P Ohri*, M Parry, E Roberts, R Subashchandran (47); *Evesham Community Hospital, Evesham* C Pycock* (2); *Fairfield General Hospital, Bury* L Aspden, L Partington-Jones, J Raw*, H Vanek, U Wadhwa (159); *Frenchay*

Hospital, Bristol R Barber, B Haywood, P Heywood*, H Lewis, K O'Sullivan, K Prout, L Whelan, A Whone (13); *Gloucestershire Royal Hospital, Gloucester* P Fletcher, E Folkes, G Fuller, P Medcalf, P Morrish*, M Silva (26); *Grantham & District Hospital, Grantham* P Aruldoss, J Farmery, K Liveley, K Shelbourn, V Sood* (1); *Hereford County Hospital, Hereford* K Bouifraden, J Dalziel*, C Evans, P Matheson, P Overstall, E Wales, G Ward (41); *Hospital Of St Cross, Rugby* J Ponsford* (1); *Ipswich Hospital, Ipswich* A Graham, SFM Grimmer*, TJ Lockington, LJ Sheehan, H Williams (8); *James Paget Hospital, Great Yarmouth* J Fuller, P Harrison, M Roche*, S Shields (2); *Kettering General Hospital, Kettering* R Glasspool, I Hubbard*, R Walters (9); *Kidderminster General Hospital, Kidderminster* C Barraclough, A McClung*, L Moseley, CK Pathirana (11); *Leicester General Hospital, Leicester* R Abbott, P Critchley, L Goodwin Wray, B Kendall, M Lawden, N Lo*, J Martey, Y Rajabally, B Simpson (45); *Leicester Royal Infirmary,* Leicester R Abbott*, P Critchley, B Kendall, M Lawden, J Martey, Y Rajabally (31); *Llandudno General Hospital, Llandudno* J Hindle*, P Ohri (10); *Luton & Dunstable Hospital, Luton* A Gale, D Phiri, L Sekaran, A Sharma*, S Wijayasiri (8); *Macclesfield District General Hospital, Macclesfield* H Fleary, A Monaghan, M Silverdale*, H Vanek, D Walker (20); *Manor Hospital, Walsall* M McGee, V Senthil*, S Reynolds (37); *Medway Maritime Hospital, Gillingham,* D Arnould, S Chong*, D Diem, B Kundu (6); *National Hospital For Neurology & Neurosciences, London* N Quinn* (2); *New Cross Hospital, Wolverhampton* H Benamer*, J Billings, R Corston, D D'Costa, M Green, J Shuri (22); *Newcastle General Hospital, Newcastle upon Tyne* T Cassidy, S Dodds, A Gani, R Lawson, J Noble* (4); *Norfolk & Norwich University Hospital, Norwich* Y Chan, K Clipsham, J Cochius, D Dick, M Hipperson, M Lee, B Payne, F Reading, M Roche*, K Sabanathan, S Shields, P Worth (43); *North Devon District Hospital, Barnstable* G Harper*, W Honan, L Oxborough, J Saunders, J Stanley (38); *North Manchester General Hospital, Manchester* P McCann* (2); *North Tyneside General Hospital, North Shields* P Edmonds, A Hand, S O'Hanlon, L Robinson, R Walker*, (21); *Northern General Hospital, Sheffield* D Bolam, B Liddle* (5); *Perry Tree Centre, Birmingham* SL Ballantyne*, R Byravan, P Jones (7); *Peterborough and Stamford NHS Trust, Peterborough* S Guptha*, C Noble, S Roychowdhury (13); *Poole General Hospital, Poole* C Ellis, R Harries-Jones*, C Hillier, N Milligan, J Potter (2); *Princess Of Wales Hospital, Bridgend* L Ebenezer, S Raha*, S Thompson (54); *Queen Elizabeth Hospital, Birmingham* H Benamer, R Crouch, K Healy, R Hornabrook, M Johnson, D Nicholl, H Pall, P Praamstra, A Williams* (49); Queen *Elizabeth Hospital, Gateshead* D Beaumont* (4); *Queen Elizabeth Hospital, Kings Lynn* S Ell*, J McGourty (2); *Queen Elizabeth The Queen Mother Hospital, Margate* M Jenkinson*, M McHenry, N Scoble, R Vahid (19); *Queen's Hospital, Romsford (formerly Harold Wood Hospital)* L Findley*, A Misbahuddin (4); *Radcliffe Infirmary, Oxford* J Adcock, A Chatterjee, H Collins, S Fairweather*, E Flossman, R Greenhall, H Hart, J Shaw, S Singh, K Talbot, S Thompson, A Weir (12); *Raigmore Hospital, Inverness* D Gray, V Sood, S Sutherland, M Wilson* (4); *Rookwood Hospital, Cardiff* T Hughes*, A Jones, L Morgan, B Sastry (4); *Rotherham District General Hospital, Rotherham* A Abdel-Hafiz*, F Al-Modaris, S Dutta, T Mallik, B Mondal, J Roberts, S Sinha (3); *Royal Bournemouth General Hospital, Bournemouth* K Amar*, S Atkins, G Devadason, A Martin, C Thompson (68); *Royal Devon & Exeter Hospital, Wonford* G Fenwick, K Gormley, N Gutowski, S Harris, T Harrower, A Hemsley, W Honan, M James, O Jeffreys, T Malone*, V Pearce, R Sheridan, C Soper, J Sword, A Zeman (251); *Royal Hampshire County Hospital, Winchester* C Gordon*, T McElwaine, V Pressly (13); *Royal Sussex County Hospital, Brighton* D Chan, R Saha* (9); *Royal United Hospital, Bath* D Howcroft, K Mugweni, D Robertson*, A Stephens, E Whelan, A Wright (37); *Royal Victoria Hospital, Dundee* N Blane, S Burns, W Mutch*, R Roberts (1); *Russian State Medical University, Russia* E Chikna* (27); *Salisbury District Hospital, Salisbury* J Chamberlain, J Lee, J Marigold* (26); *Southampton General Hospital, Southampton* J Adams, J Dulay, S Evans, J Frankel, P Garrard, W Gibb, R Gove, C Holmes, N Lawton, N Malik, T McElwaine, S Morgan, H Phipps, V Pressly, V Queen, H Roberts*, R Tan, G Turner, R Weller, S Zaman (43); *Southend Hospital, Southend* A O'Brien* (1); *Southern General Hospital, Glasgow* D Grosset*, G MacPhee, A McGonigal, C Vennard (9); *St. Anne's Teaching Hospital, Czech Republic* I Rektorova* (15); *St Peter's Hospital, Chertsey* G Carey, B Castleton, Z Dhakam*, E Kalcantera, C Long, B Mandal, V Martin, R, Nari, V Nicholas, C Sunderland (6); *St Richard's Hospital, Chichester* S Franks, S Hammans, V Moffitt, M Rice-Oxley* (21); *Stafford Hospital, Stafford* J Elizabeth, A Logan, B Summers* (7); *Taunton & Somerset Hospital, Taunton* S Cooper*, W Darch, J Homan, M Hussain, D Sharratt, T Solanki (28); *The Royal Oldham Hospital, Oldham* J Bennett, J Vassallo* (21); *Torbay District General Hospital, Torquay* A Ford, G Kendall*, K Stocker (17); *University Hospital, Coventry* A Chaudhry, A Grubneac, A Kenton, A Lindahl, J Lismore, M McConville, R Peskett, J Ponsford*, A Shehu, L Strens (5); *University Hospital Of Wales, Cardiff* T Hughes*, B Sastry (5); *Victoria Central Hospital, Wirral* J Barrett*, C Turnbull, H Vanek (3); *Walton Centre For Neurology & Neurosurgery, Liverpool* A Moore*, I O'Brien, D Watling, L Wyatt (28); *Wansbeck Hospital, Ashington* C Jones, T Mahan, K Ullyart, B Wood* (59); *Warwick Hospital, Warwick* H Desai, P Ferry, A Grubneac, J Ponsford, P Ray, P Rose, A Shehu, B Thanvi*, S Waters (7); *Watford General Hospital, Watford* S Rizvi*, A Sa'Adu, E Walker (29); *West Cumberland Hospital, Whitehaven* G Berry, N Russell* (24); *West Suffolk Hospital, Bury St Edmonds* G Lennox*, T Ward (10); *Whiston Hospital, Prescot* J Abrams*, S Ashley, M Steiger (5); *William Harvey Hospital, Ashford* A Beal, J Hawkins*, A Heller, M Jenkinson, M McHenry, M Samuel, N Scoble, R Vahid (2); *Woodend General Hospital, Aberdeen* L Caie, V Leslie, W Primrose* (5); *Worcester Royal Hospital, Worcester* M Hipperson, C Pycock* (36); *Yeovil District Hospital, Yeovil* K Baker, C Buckley, S Bulley, D Gibbons, R Goodland, P Heywood, L Jones, L Martin, M. R. Qadiri, K Rashed, R Rowland-Axe, A Stone, M Whittuck (51)

Declaration of interests

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References

1 Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. *Mov Disord* 2003; **18:** 19–31.

2 Schrag A, Ben-Shlomo Y, Quinn NP. Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. *BMJ* 2000; **321:** 21–22.

3 Oertel WH, Quinn NP. Parkinson's disease: drug therapy. *Baillieres Clin Neurol* 1997; **6:** 89–108.

4 Fahn S, Oakes D, Shoulson I, et al, and the Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004; **351:** 2498–508.

5 Stowe RL, Ives NJ, Clarke C, et al. Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database Syst Rev* 2008; **2:** CD006564.

6 Ives NJ, Stowe RL, Marro J, et al. Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ* 2004; **329:** 593.

7 Lees AJ, and the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–07.

8 The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989; **321:** 1364–71.

9 Wheatley K, Stowe RL, Clarke CE, Hills RK, Williams AC, Gray R. Evaluating drug treatments for Parkinson's disease: how good are the trials? *BMJ* 2002; **324:** 1508–11.

10 Olanow CW, Kieburtz K. Defining disease-modifying therapies for PD—a road map for moving forward. *Mov Disord* 2010; **25:** 1774–79.

11 National Collaborating Centre for Chronic Conditions. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians, 2006.

12 Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988; **51:** 745–52.

13 Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 1997; **26:** 353–57.

14 Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D—a generic quality of life measure-is a useful instrument to measure quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000; **69:** 67–73.

15 Schafer J. Analysis of incomplete multivariate data. Chapman & Hall. London, 1999.

16 Jenkinson C, Heffernan C, Doll H, Fitzpatrick R. The Parkinson's Disease Questionnaire (PDQ-39): evidence for a method of imputing missing data. *Age Ageing* 2006; **35:** 497–502.

17 Peto V, Jenkinson C, Fitzpatrick R. Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire. *Age Ageing* 2001; **30:** 299–302.

18 Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010; **25:** 2649–53.

19 Utsumi H. Long-term effects of cabergoline and levodopa in Japanese patients with early Parkinson's disease: a 5-year prospective study. *Acta Medica Okayama* 2012; **66:** 163–70.

20 Macleod AD, Counsell CE, Ives N, Stowe R. Monoamine oxidase B inhibitors for early Parkinson's disease. *Cochrane Database Syst Rev* 2005; **3:** CD004898.

21 van Hilten JJ, Ramaker CC, Stowe R, Ives NJ. Bromocriptine versus levodopa in early Parkinson's disease. *Cochrane Database Syst Rev* 2007; **4:** CD002258.

22 van Hilten JJ, Ramaker CC, Stowe R, Ives NJ. Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. *Cochrane Database Syst Rev* 2007; **4:** CD003634.

23 Caslake R, Macleod A, Ives N, Stowe R, Counsell C. Monoamine oxidase B inhibitors versus other dopaminergic agents in early Parkinson's disease. *Cochrane Database Syst Rev* 2009; **4:** CD006661.

24 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; **41:** 582–92.

25 Cohen J. Statistical power analysis for the behavioural sciences. 2nd edn. New York: Academic Press, 1988.

26 Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *Int J Geriatr Psychiatry* 2011; **26:** 812–17.

27 Food and Drug Administration. Peripheral and central nervous system drugs advisory committee meeting, July 7, 1989. Rockville: Department of Health and Human Services, Public Health Service, Food and Drug Administration, 1989: 227.

28 Caslake R, Taylor K, Scott N, et al. Age-, gender-, and socioeconomic status-specific incidence of Parkinson's disease and parkinsonism in North East Scotland: the PINE study. *Parkinsonism Relat Disord* 2013; **19:** 515–21.

29 Williams A, Gill S, Varma T, et al, and the PD SURG Collaborative Group. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010; **9:** 581–91.

30 National Institute for Health and Clinical Excellence. Review of clinical guideline (CG 35)—Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. http://www.nice.org.uk/nicemedia/live/10984/55872/55872.pdf (accessed Nov 17, 2013).